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REVIEW ARTICLE

The interplay between lymphatic system and portal hypertension: a comprehensive review

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Abstract

Background The pathophysiology of portal hypertension revolves around numerous structural and functional changes in the intra- and extra-hepatic vascular compartments. In recent years, a dysfunction of the lymphatic system has garnered increasing attention as one of the key sequelae of portal hypertension.

Purpose and Methods The review comprehensively deliberates about the anatomical and functional attributes of the hepatic lymphatic system during portal hypertension. Along with liver lymphatic system, important modifications that occur in extrahepatic lymphatics during advanced liver disease are discussed.

Results During progression of liver disease, elevated portal pressures cause increased sinusoidal blood and enhanced lymph flow, leading to dilation and proliferation of hepatic lymphatic vessels. In advanced liver disease, portal and central lymphatic systems also undergo profound changes to accommodate increased lymph flows. These changes in lymphatic system seem to have evolved as compensatory mechanisms to alleviate enhanced portal pressures. However, further increase in the splanchnic lymph production causes a complete failure of the drainage capacity of local and central lymphatic vessels, leading to maldistribution of extracellular fluid along with immune system anomalies aggravating ascites and pathological bacterial translocation.

Conclusion Lymphatic dysfunction plays a crucial role in the progression and complications of portal hypertension. Development of routine imaging techniques for lymphatic vessels in clinics, protocols for measuring lymphovenous pressure gradient and in vitro and in vivo experimental studies are requisite to further our understanding in this field. Targeting lymphatic dysfunction could offer promising therapeutic options for managing cirrhosis, portal hypertension and related complications.

Keywords Portal hypertension · Advanced liver cirrhosis · Lymphatic system · Lymphangiogenesis · Ascites

Introduction

The development of portal hypertension is one of the most critical consequences of cirrhosis. It is a pathological increase in the pressure within the portal venous system above its physiological range [hepatic venous pressure gradient (HVPG) > 5 mmHg]. HVPG ≥ 10–12 mmHg indicates clinically significant portal hypertension (CSPH) and is known to cause severe clinical complications in cirrhosis, including portosystemic shunting, variceal bleeding, ascites, hepatic encephalopathy, and renal dysfunction. The progression from cirrhosis to portal hypertension is complex and involves both structural and functional alterations within the liver and systemic circulation. Understanding the underlying causes and consequences of portal hypertension is crucial due to its significant prognostic implications in patients with advanced liver diseases [1]. Recent years have divulged the role of lymphatic vessel anomalies in liver disease and many of its associated complications [2, 3]. Lymphatic vessels run parallel to the blood vessels and are responsible for the drainage of liquids, solutes, and cells from interstitial spaces. Profound changes in both intra and extra-hepatic blood vasculature during portal hypertension have been well-reviewed [4]. However, as compared to the blood vessels, lymphatic vessels remain less studied. This review aims to provide a comprehensive and up-to-date overview of the impact of portal hypertension on lymphatic vascular biology and highlights how dysfunction of the lymphatic system governs the progression of cirrhosis and its complications.

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The lymphatic system

The lymphatic vasculature comprises an open, unidirectional and low-pressure system present throughout the body that preserves the fluid volume of our body and provides immunity against foreign invaders. In every organ, this system comprises lymphatic vessels lined with specialized lymphatic endothelial cells (LyECs) [5]. Lymphatic vessels are organized into blind-ended initial lymphatic capillaries with LyECs but without smooth muscle cell coverage and collecting vessels with both LyECs and smooth muscle cell layer. The collecting lymphatic capillaries collect the extravasated fluid (now termed as lymph) and transport it to the larger collecting lymph vessels (the right lymphatic duct and the thoracic duct) to return it to the bloodstream via subclavian veins. Initially, considered as passive conduits, these vessels have now gained paramount attention for maintaining many vital functions of the body, including extracellular fluid distribution to prevent tissue edema, sequestration of immune responses in lymph nodes, containment of bacterial infections, and tissue growth and regeneration [6, 7].

The liver produces 25–50% of total lymph entering into the thoracic duct [8]. Hepatic lymph is mainly derived from the highly permeable sinusoidal capillaries and the true capillaries of the peribiliary plexus in the liver contribute less than 10% to the total hepatic lymph output. Fluid filtered out of the sinusoids into the space of Disse flows through the channels traversing the limiting plate and enters the interstitial space [8]. This flow of sinusoidal fluid through the capillary wall into the interstitial space is governed by the balance between intravascular and interstitial oncotic and hydrostatic forces as well as the permeability of the capillary wall [9]. The hepatic lymph from sinusoids drains through three pathways: the periportal lymphatic system along the portal triad, the hepatic venous and sublobular lymphatic system along the hepatic veins, and the superficial lymphatic system of the liver capsule. About 80% or more of hepatic lymph drains into portal lymphatic vessels, while the remainder drains through sublobular and capsular lymphatic vessels [8]. All lymphatic capillaries inside the liver, irrespective of the location, ultimately join with the collecting vessels and draining lymph nodes extrahepatically, and finally the thoracic duct. In recent years, several marker proteins have been established for the identification of lymphatic vessels and LyECs in general, including the transcription factor PROX-1, the transmembrane tyrosine kinase receptor VEGFR-3, the lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1), surface glycoprotein podoplanin (PDPN) and IL-7 [10]. These markers have led to a clear distinction between blood and lymphatic vasculature. But for liver, many of these markers are also expressed by non-lymphatic cells (Table 1). Hence, studies have used a combination of markers to accurately localize hepatic LyECs and hence lymphatic vessels. The phenotype, PDPN + LYVE-1 + CK19– has been widely accepted to identify hepatic lymphatic vessels [11].

Vascular remodelling in liver during portal hypertension

Portal hypertension is the consequence of sinusoidal obstruction and increased hepatic resistance. Structural changes in a cirrhotic liver are central to the development of intrahepatic resistance and the progression to portal hypertension. The deposition of extracellular matrix (ECM) proteins, fibrosis progression to cirrhosis and the formation of regenerative

Table 1 Specific and overlapping phenotypic markers of hepatic LyECs

Markers	Gene	Location on LyECs	Cellular types other than LyECs
Prox1	*Prospero-related homeobox 1*	In nuclei of all LyEC Transcription factor [67]	Early embryonic hypoblasts Adult hepatocytes [68]
LYVE1	*LYVE1*	Transmembrane protein On overlapping flaps of LEC [69]	LSEC Macrophages[70]
Podoplanin	*PDPN*	Transmembrane glycoprotein On cell membrane of LuEC [71]	Cholangiocytes, nerve fibers in the hepatic hilum, and mesothelial cells cover the hepatic capsule [72]
VEGFR-3	*FLT4*	Transmembrane protein On cell membrane of LyEC acts as a receptor present on the surface of LyECs [73]	LSEC, pan endothelial marker[74]
CD31	*PECAM*	Transmembrane protein On overlapping flaps of LyEC and zipper-like junction [75]	Pan endothelial marker [69]
IL-7	*IL-7*	Present in cytoplasm, secreted protein [10]	Immune cells [10]

LyECs lymphatic endothelial cells, *LSECs* liver sinusoidal endothelial cells

nodules disrupt the normal lobular architecture, narrowing the sinusoidal space and increasing vascular resistance [12]. Regenerative nodules exert mechanical pressure on the surrounding vasculature, compressing small veins and sinusoids, further obstructing blood flow. These structural alterations collectively obstruct the portal venous outflow, serving as a primary cause of portal hypertension in cirrhosis. Aberrant blood flow in a cirrhotic liver damages endothelium, triggering capillarization and disrupting vascular tone by reducing nitric oxide (NO) production and increasing vasoconstrictors like endothelin-1 and angiotensin II [13]. These factors, along with others, are also responsible for stellate cell activation, triggering their transformation into myofibroblast-like cells, which not only exacerbate hepatic fibrosis but also further increase intrahepatic vascular resistance and aggravate portal hypertension [14].

Lymphatic vascular system adaptations in cirrhosis and portal hypertension

Hepatic sinusoids possess a discontinuous endothelium lining. This characteristic feature creates large gaps within sinusoidal membrane, allowing relatively free passage of plasma protein into the surrounding hepatic interstitium. Consequently, the oncotic pressure within the tissue approaches that of plasma, resulting in a minimal oncotic pressure gradient normally operating across the hepatic sinusoid. The fluid filtration in the liver is restrained by an extraordinarily low sinusoidal pressure (5 mmHg), and even a slight increment of hydrostatic pressure can trigger a significant and rapid outflow of both solute and water into the surrounding space. Owing to structural and dynamic changes in liver vascular system in cirrhosis and portal hypertension, there is an increased sinusoidal hydrostatic pressure that causes an increase in the hepatic and thoracic duct lymph flow (Fig. 1). A decreased plasma oncotic pressure, i.e., hypoalbuminemia, also increases lymph flows. The thoracic duct lymph flow is 3–6 fold higher and hemorrhagic in patients with cirrhosis than the normal rate of 1 ml per minute flow in healthy subjects [15]. To accommodate increased lymphatic flows, the formation of new lymphatic vessels i.e. lymphangiogenesis occurs to drain the excessive fluid and reduce the portal pressures (Fig. 1) [16]. A histology study in human chronic viral liver disease illustrated that the number and area of lymphatic vessels were increased in accordance with the degree of liver fibrosis [17], but neither showed any relationship with the degree of activity of hepatitis. In another clinical study in patients with primary biliary cirrhosis, [18] it was demonstrated that the number of hepatic lymphatics are increased even at an early stage in these patients. This study showed that the number of lymphatic vessels within the portal tract are strongly correlated with the degree of portal tract expansion, indicating a strong correlation between lymphatic vessel proliferation and disturbance of the microcirculation associated with portal hypertension. It is now clearly documented that irrespective of etiology, there is an increased number of dilated PDPN+ hepatic lymphatic vessels in and around the portal areas in patients with liver disease. These vessels are in close proximity to T cells and macrophages, thus confirming their location to areas of active inflammation and fibrosis [19]. In a recent study conducted in 45 liver biopsies collected from patients with various stages of NAFLD and NASH, there was an increased expansion of lymphatic vessels as measured by PDPN staining with the progression of disease, clearly suggesting that the expansion of the liver lymphatic vasculature during end-stage liver disease is not merely a consequence of cirrhosis [11]. Interestingly, a study conducted from liver wedge biopsies taken immediately below the liver capsule in patients with idiopathic portal hypertension (IPH) and healthy subjects revealed an increased number of hepatic lymph vessels in the patients of IPH compared to controls [20]. The study also observed a reduction in the total area of branches of the portal vein. IPH is characterized by the presence of portal hypertension without evidence of cirrhosis on liver biopsy. The study findings suggesting increased density of hepatic lymphatics during IPH clearly imply that changes in the portal system that influence fluid dynamics in the liver even in the absence of liver cirrhosis can disrupt normal blood flow in the portal veins and increase hepatic lymph flow to decompress the portal vein and alleviate the portal pressures. Another study suggested that during the development of cirrhosis into acute-on-chronic liver failure (ACLF), a hyperinflammatory leads to apoptosis and dysfunction of LyECs. This dysfunction seems to be mediated by secreted phosphoprotein 1 (SPP1) secreted by the infiltrating monocyte/macrophages in ACLF livers [21]. This implicates a complete failure of the hepatic lymphatic system in ACLF.

Phenotypic and functional changes in the lymphatic vessels are also accompanied by many molecular changes in the LyECs during liver disease progression [22]. Single-cell mRNA sequencing studies on sorted LyECs from a high fat and high cholesterol-induced NASH murine model, reported that although PDPN+ lymphatic vessels expand during liver injury, there occurs a significant decline in the expression of lymphatic lineage-specific genes, PROX1 and FLT4/VEGFR3 and lymphatic drainage function to nearby draining lymph nodes. LyECs from high-fat diet models had increased expression of lipid transporter, CD36 and permeability regulator, VE-cadherin (*Cdh5*) expression as compared to controls [11]. Together these data indicate that although LyECs undergo dynamic changes in a diseased liver in terms of both structure and drainage functions.

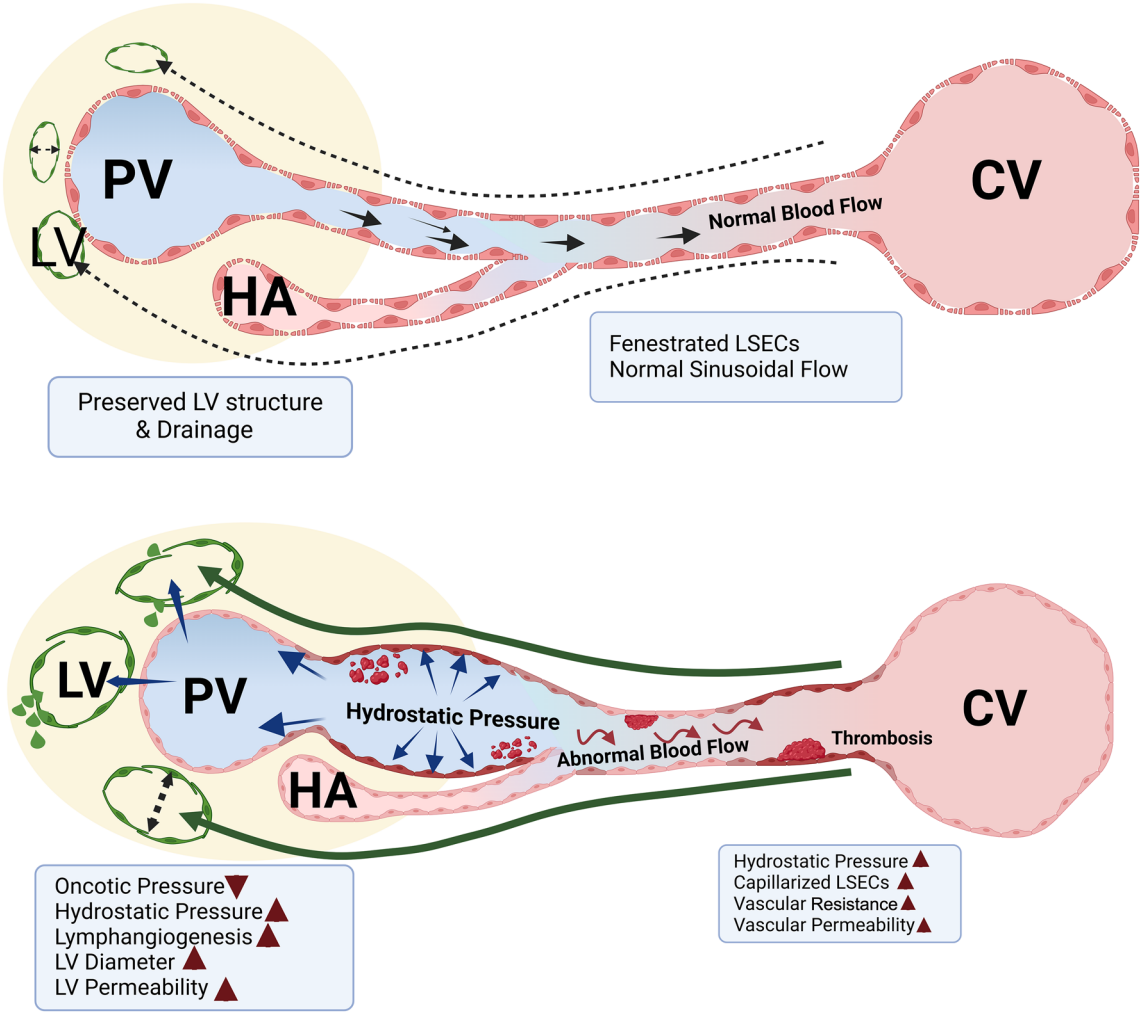

Fig. 1 Remodelling of hepatic lymphatic vessels in response to cirrhosis and portal hypertension: in healthy conditions, normal portal blood flow sustains the liver's sinusoidal structure and maintains normal lymphatic drainage. However, portal hypertension disrupts this balance. The modified sinusoid structure, abnormal blood flow within the sinusoids elevates hydrostatic pressure, causing sinusoidal capillarization. This further increases hydrostatic pressure within the lymphatic vessels while simultaneously decreasing oncotic pressure. These changes stimulate increased lymph production, lymphangiogenesis, and, impaired lymphatic drainage function. *PV* portal vein, *HA* hepatic artery, *LV* lymphatic vessels, *CV* central vein, *LSECs* liver sinusoidal endothelial cells

Extra-hepatic blood vascular changes in portal hypertension

While intrahepatic factors play a significant role in the genesis of portal hypertension in cirrhosis, extra-hepatic factors contribute to the exacerbation and persistence of elevated portal pressures. Despite increased intra-hepatic resistance, within the splanchnic and systemic circulation there is increased cardiac output in response to decreased systemic vascular resistance. Hence, as a secondary event, portal hypertension induces splanchnic and systemic arterial vasodilation leading to the development of a hyperdynamic circulatory syndrome [4]. The diminished systemic vascular resistance is largely the result of a decrease in splanchnic arterial resistance owing to splanchnic vasodilation, which is caused due to increased production of local and systemic vasodilators such as eNOS-derived NO, arachidonic metabolites, carbon monoxide, and endocannabinoids (Fig. 2) [23]. Increased expression of NO and pro-angiogenic factors such as VEGF is also reported to facilitate the formation of porto-systemic collaterals (or shunts) in the mesenteric and splanchnic vascular beds through the opening of pre-existing vessels. The splanchnic vascular remodeling and angiogenesis is actually an attempt to relieve the excess portal pressure and allow decompression by redistributing flow through esophageal and hemorrhoidal collaterals. Splanchnic vasodilation and angiogenesis, contribute significantly to serious complications of cirrhosis. The development of collaterals facilitate the formation of varices and allows the delivery of noxious substances from the portal circulation directly to

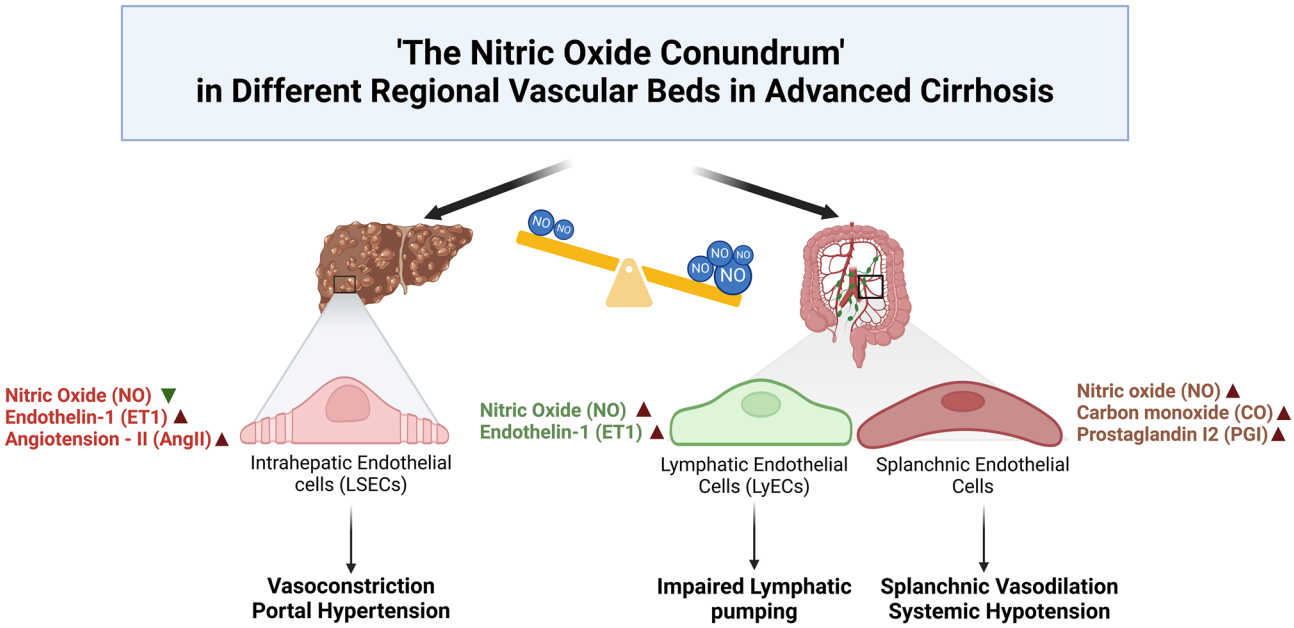

Fig. 2 The nitric oxide (NO) conundrum in portal hypertension: in homeostasis, an equilibrium exists between NO production and its physiological requirement within the intrahepatic, splanchnic and lymphatic circulation. However, in the context of portal hypertension, this balance is disrupted. There is a relative deficiency of NO in the intrahepatic circulation and an aberrant increase in the splanchnic and lymphatic beds. This incongruity leads to paradoxical vascular responses; hepatic vasoconstriction due to NO deficiency and splanchnic and lymphatic vasodilation driven by excessive NO. Known vasoactive factors in hepatic and splanchnic bed include endothelin-1, angiotensin, carbon monoxide and prostaglandins

the cerebral vasculature without hepatic detoxification, thus contributing to hepatic encephalopathy [4, 24].

Extra-hepatic lymphatic vascular system in portal hypertension

As portal pressure continues to rise in patients with cirrhosis, significant alterations also become evident in the extra-hepatic gut lymphatics. Overall, lymph flows from the intestine and liver in cirrhotic animals increase threefold and 30-fold, respectively, over values obtained from control animals with a good correlation between intestinal and liver lymph flows with portal venous pressure [25]. In the splanchnic circulation of cirrhosis patients, arteriolar vasodilation increases the production of splanchnic lymph. The hyperdynamic state of the splanchnic circulation, characterized by increased blood flow, combined with an abnormal fluid balance across the gut wall (altered oncotic gradient), further enhances lymph production and drainage. When the splanchnic lymphatic system becomes overwhelmed, exceeding its capacity to transport this excess fluid, lymph fluid leaks into the peritoneal cavity, contributing to the development of ascites and edema (Fig. 3). Ribera et al. performed fluorescent lymphangiography in the peripheral (tail, ear, footpad) and splanchnic regions using FITC-dextran and the fluorescent lipid tracer, BODIPY FL-C16 and clearly displayed impaired drainage of lymphatic vessels in all these beds in cirrhosis [26]. The study also reported a scarce coverage of smooth muscle cells (SMCs) on the mesenteric collecting lymphatic vessels in cirrhosis. This, according to the authors led to an impaired mesenteric lymph flow in the splanchnic regions. Molecularly, this was attributed to the overexpression of eNOS and the production of NO by cirrhotic LyECs [27]. Hence, in response to altered blood flow and shear stress, an increased NO production not only takes place in the mesenteric arterial vascular endothelium but also in the mesenteric LyECs in portal hypertensive animals (Fig. 2) [28]. In one of our clinical studies, we have also reported the presence of duodenal lymphangiectasia, i.e. an increased number of dilated PDPN+ lymphatic vessels/lacteals in the duodenal biopsies of patients with decompensated liver cirrhosis and ascites [29]. Patients with high PDPN immuno-histochemistry scores (> 6.5) had higher 3-month mortality than those with lower scores. An increased number of dilated PDPN+ intestinal lymphatic vessels in cirrhotic patients implicates an impairment of intestinal lymph drainage followed by compensatory lymphangiogenesis.

Increased lymph flow from both the gut and liver ultimately drains into the thoracic duct (TD). TD is the largest lymphatic duct, that drains about 75% of the body's lymph into the bloodstream via the left subclavian vein.

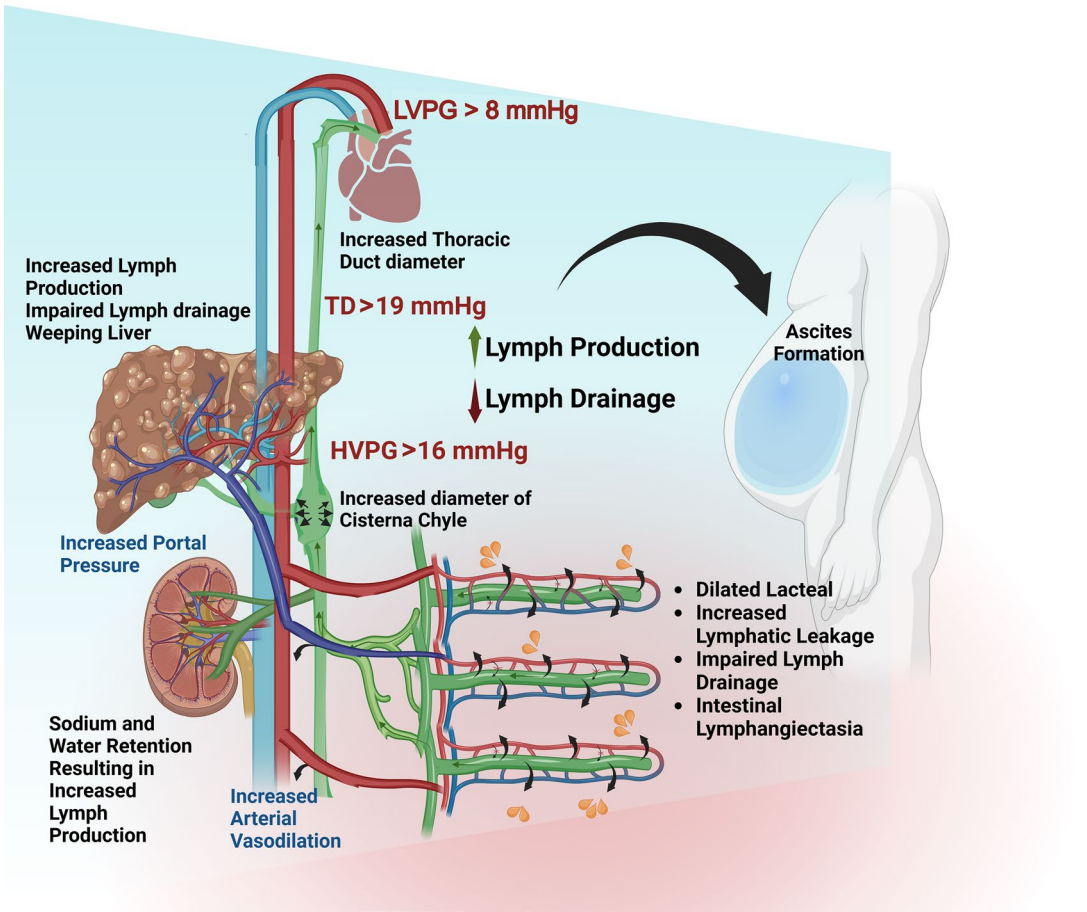

Fig. 3 Lymphatic in ascites development: in cirrhotic patients with ascites and portal hypertension, elevated hepatic venous pressure gradient (HVPG) increases splanchnic blood flow and lymph production. This heightened lymphatic load distends lymphatic vessels and the cisterna chyli, raising the thoracic duct (TD) and lympho-venous pressure gradient (LVPG). However, overwhelmed lymphatic vessels eventually compromise lymphatic uptake, leading to lymph leakage. This imbalance between amplified lymph production and impaired lymphatic drainage results in excess fluid accumulation within the splanchnic compartment, ultimately contributing to the development of ascites

TD originates from a widened segment called the cisterna chyli (CC), which accumulates lymph from the lumbar and intestinal trunks. A study demonstrated a significant elevation of TD pressure in cirrhotic patients, with a mean end pressure of 20 mmHg versus 8.5 mmHg in non-cirrhotic patients [30]. Lymphangiography studies have shown that both portal lymphatics and the cisterna chyli are dilated in patients with portal hypertension [31]. Piper et al. reported that as compared to patients with large portosystemic collaterals, patients without large collaterals exhibited significantly larger CC diameters showing a strong correlation with portal pressure. This implies that there are more lymph flows within the CC in patients as a compensatory mechanism due to the lack of decompression via larger venous collaterals [32]. A study by Yano et al. conducted an interesting single-center retrospective cross-sectional study to determine the diameters of TD and CC in patients with advanced chronic liver diseases (ACLD) by ultrasonography and computed tomography [33]. By setting specific cutoff values (rule-in/rule-out CC: > 5.4 mm, < 4.5 mm; rule-in/rule-out TD: > 3.7 mm, < 2.1 mm), the authors suggested that CC or TD maximum diameters can be combined with Baveno-VII criteria to achieve a more comprehensive and accurate stratification of ACLD patients [34]. The dilated CC and TD in ACLD could be attributed to increased portal pressures and the volume of lymph fluid passing through them. The study also indicated chronological changes in the diameter of TD and CC. On 2-year follow-up of 76 patients, the authors noted that CC diameter initially enlarged and then narrowed at a later point, particularly of those patients with a higher risk of developing serious complications such as refractory ascites, variceal bleeding, and hepatic

encephalopathy [35]. The study also reported that this narrowing of the extra-hepatic lymphatic vessels was irreversible and did not improve even after treating ascites. The study suggested that the narrowing of CC or TD might be associated with decompensation of CSPH. An autopsy from a refractory ascites patient has shown a thickened SMC layer in TD [33]. Thus, it can be inferred that excessive lymphatic flow due to sustained portal hypertension causes excessive proliferation of SMC of lymphatic vessels and thickening of the vessel walls, narrowing of the TD lumen and obstruction of lymph flow. A narrowing of lymphovenous junction (LVJ), between the TD and the left subclavian vein (LSV) has been documented in a cadaveric series, which may limit thoracic duct lymph flow and be responsible for enlarged TD diameter [36]. Patients with cirrhosis and portal hypertension have been shown to have a significant lymphovenous pressure gradient (LVPG) between TD and LSV [37]. LVPG refers to the difference in pressure between a lymphatic vessel (e.g., thoracic duct) and a nearby vein (e.g., left subclavian vein). It essentially indicates the pressure difference that drives lymph fluid from the lymphatic system into the bloodstream. For the measurement of LVPG, the pressure is first measured in the TD (using the first 4-F catheter in the TD). The second catheter is positioned in the left subclavian vein (from a second basilic or brachial venous access), and pressure is measured in the subclavian vein to calculate an LVPG [38]. A low LVPG indicates a normal healthy condition, as it means the pressure in the lymphatic vessels (lymph) is significantly lower than the pressure in the veins, allowing for proper fluid drainage from the lymphatic vessels into the bloodstream; a high LVPG, on the other hand, implies impaired lymph drainage and lymphedema. Thus, assessment of LVPG can inform about lymphatic drainage dysfunction.

In addition to altered LVPG, studies have demonstrated a significant increase in lymphatic conductance within the thoracic duct in cirrhotic patients without ascites as compared to controls. Conversely, these values were decreased to near-normal in patients with tense ascites [39]. These observations convey how different modifications in the lymphatic vessels might govern the development of ascites and other complications in patients with ACLD. It may be thus summarized that when augmented hepatic and intestinal lymph flow into the peritoneal cavity is not matched by increased re-absorption into the systemic venous system via hepatomesenteric-diaphragmatic and central or TD lymphatics, the renin-aldosterone system in the kidneys gets activated, leading to abnormal renal sodium and water retention, further aggravating lymph imbalance and clinical ascites and ultimately the hepatorenal syndrome (Fig. 3) [40]. An increased splanchnic vascular permeability and chronic retention of renal sodium and water then plays a major role in the sustained development of ascites [41].

Overtime, with persistently high lymphatic pressure associated with portal hypertension, dilated lymphatic channels in the small intestine have also been reported to rupture causing the leakage of lipid-rich lymph into the peritoneal cavity in cirrhosis patients. These ascites have a milky appearance and a triglyceride level of > 200 mg/dL and is termed as chylous ascites [42]. Rupture of intestinal lymphatic channels with subsequent loss of lymph in the intestinal lumen can result in hypoproteinemia, lymphocytopenia, and malabsorption of fat. In addition, loss of lymphocytes may contribute to an increased susceptibility to infections in cirrhosis. This complication, called as protein-losing enteropathy (PLE) arises when the rate of protein loss into the gut exceeds the rate of protein synthesis by the liver. PLE is a life-threatening disease and affects 3–18% of patients after a Fontan operation, a palliative surgical procedure performed in children with univentricular hearts. Hence, although intestinal lymphangiectasia can be present in all patients with end-stage cirrhosis, sustained portal hypertension can contribute to the rupture of the lacteals and the development of severe hypoalbuminemia and PLE in a few of them [43]. In patients with PLE, protein loss in the intestinal lumen can further lead to an increase in ascites. The exact prevalence of PLE in patients with cirrhosis and portal hypertension has not however been systematically investigated in large studies.

Lymphatic vascular system and extra-hepatic complications of portal hypertension

Portal hypertension can result in spontaneous or surgical formation of mesocaval shunts, enabling the direct translocation of pathogens and toxins from the mesentery into the lungs. Although the formation of portocaval or mesocaval shunts alleviates the portal pressure yet allows the direct translocation of toxins from the mesenteric circulation into the systemic circulation without passing the liver. These changes are responsible for the development of extra-hepatic complications like pulmonary vascular disorders, such as hepatopulmonary syndrome (HPS) and portoplumonary hypertension (PoPH) and hepatic encephalopathy (HE) in patients with portal hypertension. HPS is characterized by abnormal dilation of blood vessels in the lungs leading to low oxygen levels (hypoxia), while PoPH results from vasoconstriction and remodeling of pulmonary arteries, causing high blood pressure in the lungs (pulmonary hypertension) due to increased vascular resistance. HPS involves too much blood flow in the lungs with poor oxygen exchange. In contrast, POPH involves restricted blood flow through narrowed pulmonary arteries, leading to elevated pulmonary pressure and

potential right heart failure. Some HPS patients also show hepatic hydrothorax (HH) as a secondary complication. The pathogenesis of HH involves the movement of ascitic fluid into the pleural space. Patients with severe HPS, PoPH and HH have increased mortality and require liver transplantation.

Along with the portal system, the lymphatic system significantly accounts for the physiological and pathological translocation of pathogens, its molecules, and toxins into distant organs such as the lungs. Mesenteric lymph that enters systemic circulation via the thoracic duct, empties into the subclavian vein, thus making the lung the first organ exposed to mesenteric lymph. Studies in rats subjected to trauma (laparotomy) and hemorrhagic shock have shown that gut-derived inflammatory factors contained in the mesenteric lymph, rather than those in the portal vein, cause lung injury [44]. In trauma-hemorrhagic shock models, mesenteric lymph was found to induce injury to pulmonary microvascular endothelial cells and increase lung permeability [45]. Importantly, the pulmonary injury induced by hemorrhagic shock was alleviated by ligation of the mesenteric lymph duct [46]. This mode of injury to the lung, which is caused by gut-derived inflammatory factors contained in the mesenteric lymph, has been named the "gut lymph-lung axis" [47].

Although the role of gut lymphatics is not much explored in HPS, HH, and PoPH, it is logical to hypothesize that in cirrhosis, gut microbiome dysbiosis and disruption of gastrointestinal barriers in these complications cause enhanced translocation of bacterial and other damaging non-bacterial toxins from the gut into the systemic circulation and lungs via the mesenteric lymph. Given the fact that changes in lymphatic morphology or function have been observed in nearly every lung disease, discrete changes in the structure and function of lung lymphatic vessels in patients with HPS, HH, and PoPH are also expected [48]. It is important to note that portocaval and mesocaval shunts that increase the levels of gut toxins, including ammonia and other bacterial products in the systemic circulation, also increase the risk of HE. Intriguingly, one of the major pathogenesis mechanisms of HE involves an impaired clearance of ammonia by the brain's lymphatic system. The accumulation of metabolic waste products and noxious substances in the interstitial fluid of the brain due to dysfunctional lymphatic vessels has been reported to contribute to neuronal dysfunction and cognitive impairment in HE [49]. In this regard, the mechanisms by which mesenteric lymph-derived factors cause pulmonary injury and analysis of local lung lymphatic vessels in experimental models of portal hypertension warrant further investigations.

Bacterial translocation, lymph nodes and portal hypertension

While liver ECM deposition, architectural changes and extra-hepatic vascular remodeling remain crucial for pathogenesis and progression of portal hypertension, the newer paradigm emphasizes the importance of gut-liver axis and pathological bacterial translocation (BT) in the exacerbation of portal pressures [50]. The gastrointestinal tract comprises of the largest surface area of the body with an epithelial surface of approximately 400 m^2 and is in constant exposure to live commensal bacteria. Gut epithelial and vascular barriers along with immunity play major roles in defence by inhibiting the translocation of bacteria to systemic circulation. The integrity of epithelial barriers is maintained by tight junctions, adherence junctions and desmosomes under homeostatic conditions. The intestinal and mesenteric lymphatic vessels serve as conduits for the trafficking of gut bacteria, bacterial products and leukocytes from peripheral sites to their draining mesenteric lymph nodes (MLNs) [51]. MLNs thus act as immune hubs and powerful barriers to contain the spread of pathogens in the systemic circulation. An increased passage of bacteria and/or bacterial products into MLNs is termed as pathological BT. In experimental models, BT is defined as a MLN-positive culture and has been seen in about 50–60% of rats with carbon-tetrachloride (CCl_4)-induced cirrhosis and ascites [52]. Patients with Child–Pugh C cirrhosis have been shown to have bacterial growth while Child–Pugh A cirrhosis patients do not show bacterial presence in MLNs [53]. Traditionally, it was thought that BT is a characteristic feature of patients with advanced cirrhosis and spontaneous bacterial peritonitis (SBP), the presence of bacterial infection in ascites. In experimental studies, it was illustrated that green fluorescent protein (GFP)-labelled Escherichia coli when administered orally to cirrhotic rats could be seen not only in the intestinal lumen but also in the MLNs and ascites [54]. A recent study however demonstrated that systemic markers of BT like the presence of bacterial antigens were similar in patients with compensated and decompensated liver disease. They concluded that that BT might be an early even in liver disease, that triggers a selective inflammatory response, independent of hepatic damage progression. The study also showed no meaningful correlation of BT markers with HVPG and other measures of systemic hemodynamics [55]. In another study, BT was investigated at two stages of experimental portal hypertension: acute (when shunting is minimal); and chronic (when shunting is extensive and mimics the portal hypertension of cirrhosis) [56]. The authors of this study found that BT is a frequent event in the acute portal hypertension

model probably because of a greater mesenteric inflammation; however, there was no difference in the rate of BT in chronic portal hypertensive rats (15 days after portal vein ligation) compared with control rats. It was also shown that in patients with cirrhosis and ascites, the presence of bacterial DNA in serum had the same degree of portal hypertension than patients without bacterial DNA [57]. Hence, portal hypertension alone may not be a lone factor in the development of BT and vice-a-versa in cirrhosis. The severity of gut dysbiosis, gut leakiness along immune dysfunction might be other causative factors affecting the severity of BT. It may be inferred that portal hypertension and BT act as independent factors affecting liver disease severity and together they result in even more hazardous consequences. Increased BT and blood LPS levels are known to exacerbate portal hypertension even in the absence of liver cirrhosis, implicating that in the presence of pathological BT, portal hypertension worsens further [58]. In summary, defective immune responses in the liver and MLNs increased BT along with coexistence of endothelial dysfunction and vascular complications in advanced cirrhosis leads to an overall system failure to contain local bacterial infections, causing their systemic spread along with inflammatory mediators, hence resulting in the development of bacterial sepsis and other complications in advanced cirrhosis. It would be worthwhile to explore how gut lymphatic dysfunction and defective bacterial trafficking from gut lymphatics to MLNs affect portal hypertension per se in advanced cirrhosis.

Lymphatic system as a target to treat portal hypertension

Maneuvers that effectively restore lymph dynamics by either reducing intestinal lymph formation (e.g., portacaval shunt) or accelerating lymph return (e.g., peritoneovenous shunt) have been shown to improve full-blown ascites and portal hypertension [59]. In a study of 20 patients with cirrhosis, Dumont clearly established that in patients having massive ascites, following lymphatic drainage by venting the TD, ascites reduced considerably within 48–72 h [60]. These effects were similar to that seen after a successful portacaval shunt where when extra-hepatic portal hypertension was relieved, TD lymph flow decreased while protein content was enhanced. The shunt eliminated excess capillary filtrate from the extra-hepatic portal bed and also reduced excess capillary filtrate from the liver, thus reducing lymph formation. To improve lymph outflows from the TD to venous circulation, Ghelfi et al. reported 2 cases of TD stenting in patients with refractory ascites that reduced the pressure gradient between TD and left subclavian vein improving local fluid drainage [61]. In both patients, ascites were resolved within six months. In another pilot study by the same group, the same approach was utilized in 9 patients with refractory ascites. The study showed 30% clinical success i.e., no further requirement of paracentesis and no adverse events in any patient [38]. The median TD pressure decreased from 19 mmHg at the beginning of the procedure to 6 mmHg after TD stent placement but there was no major change in the HVPG of patients after stent placement [38]. Importantly, LVPG decreased from 8 to 0 mmHg resulted in attenuation of abdominal ascites and edema in the patients. Decreasing lymphatic hypertension may thus allow for more efficient TD flow [62]. Therapies that relieve obstruction of lymph outflow and ameliorate LVPG seem to have promising clinical benefits at least in some of the end-stage liver cirrhosis patients with limited treatment options [63].

A study on cirrhotic patients with dilated CC has reported that the diameter of the chyli is significantly decreased due to a reduction in hepatic lymph production after transjugular intrahepatic portosystemic shunt (TIPS) [32]. A decline in portal pressure after TIPS may be partly attributed to a reduction in hepatic lymph production and decompression of the central lymphatic system. The pumping defect due to reduced SMC coverage and associated impaired drainage in the gut or mesenteric lymphatic vessels was shown to be improved by using an eNOS inhibitor, L-NG-methyl-L-arginine (L-NMMA) as a therapy [26]. In preclinical models of liver cirrhosis, the use of L-NMMA as a treatment strategy ameliorated mesenteric lymphatic contractility and drainage increased SMC coverage on lymphatic endothelial cells, and reduced abdominal ascites volume, proving that NO inhibition can correct lymphatic dysfunction in cirrhosis. The study however did not evaluate the effect of L-NMMA on portal pressures. Another favourable approach to correct lymphatic dysfunction is to directly provide widely known pro-lymphangiogenic growth factors, which interact specifically with LyECs, resulting in the growth of new and functional lymphatics. A recombinant form of VEGF-C C165S (rVEGF-C), in which Cys156 is replaced by a Ser residue, binds only to VEGFR-3 homodimers on LyECs rather than binding to both VEGFR-2 and VEGFR-3 [64]. rVGEF-C has emerged as one of the promising and specific growth factors to induce lymphangiogenesis [65, 66]. In our studies, we used rVEGF-C, encapsulated within lipid nanoparticles for sustained release and direct uptake in lymphatic vessels [66]. This formulation was provided orally in cirrhotic animal models to specifically target the gut and mesenteric lymphatic vessels, which resulted in increased mesenteric lymphatic drainage, ascites volume, and systemic endotoxemia. Importantly, we showed that treatment with rVEGF-C also ameliorated portal pressures in non-cirrhotic portal hypertensive rats, indicating improved lymph flow dynamics can reduce portal pressures and its subsequent complications.

Conclusion

To summarize, during portal hypertension, remodelling and re-arrangements not only occur in the blood vascular system of the scarred liver or in the congested digestive tract but also parallelly in the liver and portal lymphatic drainage system. Many compensatory mechanisms such as dilation of lymphatic vessels and lymphangiogenesis occur to fulfil the demands of increased lymph flow to prevent decompensation. However, with a further increase in portal pressures and remodeling of the portal vascular system, an imbalance between the rate of formation and absorption of visceral lymph ensues. At this time, abdominal ascites, edema and decompensation becomes inevitable. This is further complicated by changes in lymph flow and drainage of the central lymphatic system. Therefore, drugs that augment lymphatic permeability, lymphatic contractions and/or improve drainage function or outflow into venous system can serve as ideal candidates for the treatment of patients with decompensated cirrhosis. In patients with ACLD, along with HVPG, it might be valuable and pertinent to measure LVPG to gain insights into the status of lymph flow and lymphatic impairments. Anomalies in the liver and intestinal lymphatic system and lymph nodes also compromise local immune responses leading to increased bacterial translocation and development of sepsis in advanced cirrhosis. A right modulation of the lymphatic system has enormous potential to redistribute the extracellular fluid volume and also empower the local immune system serving as a bastion against infections. The development of routine imaging techniques for lymphatic vessels in clinics, protocols for measuring LVPG and TD pressures and in vitro and in vivo experimental studies are requisite to further our understanding in this field and design lymphatic system targeted therapies for ACLD. With new advancements in the landscape of lymphatic system in liver diseases, numerous potential strategies for treatment and prevention await thorough exploration.

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Declarations

Conflict of interest Pinky Juneja, Rajni Yadav, Dinesh M Tripathi, Savneet Kaur have not disclosed any competing interests.

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